REVIEW

Tropical malabsorption

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Malabsorption is an important clinical problem both in visitors to the tropics and in native residents of tropical countries. Infections of the small intestine are the most important cause of tropical malabsorption. Protozoal infections cause malabsorption in immunocompetent hosts, but do so more commonly in the setting of immune deficiency. Helminth infections occasionally cause malabsorption or protein-losing enteropathy. Intestinal tuberculosis, chronic pancreatitis and small-bowel bacterial overgrowth are important causes of tropical malabsorption. In recent years, inflammatory bowel disease and coeliac disease have become major causes of malabsorption in the tropics. Sporadic tropical sprue is still an important cause of malabsorption in adults and in children in South Asia. Investigations to exclude specific infective, immunological or inflammatory causes are important before considering tropical sprue as a diagnosis. This article briefly reviews the management of tropical sprue and presents an algorithm for its investigation and management.

Malabsorption is an important clinical problem in tropical countries, typically presenting with chronic diarrhoea, glossitis, weight loss and multiple nutritional deficiencies. The typical presentation is now less common as investigation now leads to diagnosis before the full-blown clinical syndrome. The aetiological profile of malabsorption in tropical countries often differs from that in temperate zones. A description in the ancient Indian medical treatise, *Charaka samhita*, of an illness characterised by chronic diarrhoea and weight loss and attributed to failure of the digestive system[1] suggests that the malabsorption syndrome was clinically recognised in the tropics two millennia ago. In 1759, William Hillary described a malabsorption syndrome in expatriates living in Barbados,[2] but the first case that he described may have been due to giardiasis rather than tropical sprue.[3] The term sprue was introduced by Manson in 1880 and was derived from the Dutch ''Indische Sprouw'', which denoted the mouth ulcers and glossitis accompanying the condition.[4] Tropical sprue was an illness with considerable morbidity and mortality. Initially thought to be confined to visitors to the tropics, it became apparent in the early 20th century that indigenous residents of the tropics were afflicted with similar illnesses.[5] Epidemics of malabsorption, noted among armed forces and prisoners of war in the Indo-Burma theatre during World War II[6 7] and in south India in the 1960s to the early 1980s,[8] have now disappeared. In the past two decades, the profile of malabsorption has changed in tropical countries, probably related to changes in hygiene and sanitation. This review considers tropical malabsorption as any syndrome of malabsorption that affects indigenous residents of tropical countries and also travellers visiting or residing in the tropics.[9] Broadly, tropical malabsorption is categorised as (1) primary or idiopathic, where no cause is ascertained; and (2) secondary, where a definitive causative factor is identified (box 1).

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TROPICAL MALABSORPTION WITH KNOWN AETIOLOGY

Small-bowel mucosal disease

Infectious causes

Protozoal infections

Protozoal infections of the small intestine are particularly common in tropical countries and may be associated with malabsorption. In general, most such infections are self-limiting. Protozoa are an important cause of traveller's diarrhoea. Chronic diarrhoea and malabsorption are seen in a small proportion of infected people.

Giardia intestinalis is the protozoan parasite most commonly associated with malabsorption. Infection with this protozoan is common in the tropics and is often a cause of diarrhoeal illness in visitors to the tropics. *Giardia* infection usually remains asymptomatic in indigenous residents of the tropics but may sometimes cause self-limited acute diarrhoea and occasionally a malabsorption syndrome that mimics tropical sprue.[10] *Giardia* isolates from asymptomatic and symptomatic people cannot be differentiated from each other; thus, host immunity seems to be the major determinant of whether infection remains asymptomatic or becomes symptomatic.[11 12] Decreased brush-border surface area in the jejunum leads to carbohydrate malabsorption, whereas bacterial overgrowth in the small bowel with bile salt deconjugation leads to steatorrhoea.[13] The diagnosis is made by microscopic examination of fresh stool specimens or duodenal or jejunal fluid. The presence of *Giardia* cysts in the stool indicates infection. In patients with diarrhoea, trophozoites in stool are usually present. Examination of at least three faecal specimens is recommended for optimal diagnosis of the infection. A small-bowel biopsy specimen shows the parasites in the mucus layer over the epithelium, whereas the mucosa usually shows atrophy of villi and elongation of crypts with a

Abbreviations: IPSID, immunoproliferative small intestinal disease

Box 1: Causes of tropical malabsorption

With known aetiology
- Small intestinal disease
  - Infectious
    - Protozoa
      - *Giardia intestinalis*
      - *Isospora belli*
      - *Cryptosporidium parvum*
      - *Enterocytozoon bieuneusi*
      - *Encephalitozoon intestinalis*
      - *Cyclospora cayetanensis*
      - *Leishmania donovani*
    - Helminths
      - *Strongyloides stercoralis*
      - *Capillaria philippinensis*
    - Bacteria
      - *Mycobacterium tuberculosis*
    - Viruses
      - Human immunodeficiency virus
  - Inflammatory and immune related
    - Coeliac disease
    - Crohn's disease
    - Primary immunodeficiency
  - Malignant
    - Immunoproliferative small-intestinal disease and small-intestinal lymphoma
- Pancreatic disease
- Tropical pancreatitis

Unknown aetiology
- Tropical enteropathy
- Tropical sprue

mononuclear inflammatory cell infiltrate in the lamina propria. The epithelial cell damage, characterised by loss of intestinal brush-border surface, seems to be mediated by CD8 T cells.[14] Symptomatic giardiasis responds quickly to treatment with either metronidazole or tinidazole.[15] Nitazoxanide is a newer agent that can be used in the treatment of giardiasis.[16]

Other protozoa (box 1) associated with malabsorption include *Cryptosporidium parvum*, *Isospora belli*, *Cyclospora cayetanensis* and Microsporidia species (*Enterocytozoon bieneusi* and *Encephalitozoon intestinalis*). In immunocompetent people, infection with these parasites is often either asymptomatic[17] or associated with self-limited acute diarrhoea. However, immunocompetent people also sometimes show prolonged symptoms. For example, diarrhoea was shown to last for more than 2 weeks in 45% of Brazilian patients with acute cryptosporidiosis.[18] A similar prolonged diarrhoea with *Cyclospora* infection has been noted in travellers to Nepal.[19] Infection with these parasites must be first excluded as a cause of malabsorption, especially in returned travellers. Before the AIDS epidemic, these protozoa were recognised as the causes of malabsorption mainly in patients with primary immunodeficiency syndromes such as common variable immunodeficiency, and were thus relatively uncommon. Since the advent of AIDS, protozoal infections have become important causes of tropical malabsorption,[20 21] although they are now uncommon in the developed countries as a result of antiretroviral treatment.[22] There is wide regional variation in the prevalence of individual protozoal infections. For instance, *C parvum* is the most important diarrhoeal pathogen in Zaire and Uganda, whereas *I belli* is the most common pathogen causing chronic diarrhoea and malabsorption in south India.[23–25] In a patient with chronic diarrhoea and weight loss, clinical pointers to underlying HIV infection include a history of sexual promiscuity and the presence of odynophagia resulting from associated oesophageal candidiasis. Algorithms for the management of malabsorption in the tropics require that HIV illness be first excluded by appropriate testing. *I belli* infection is endemic in many parts of Africa, Asia and South America,[26] and 5–10% of stool specimens in Asia and Africa are positive for cryptosporidia.[27] Paromomycin, and more recently nitazoxanide, is useful in the treatment of diarrhoeal illness associated with cryptosporidia.[28 29] *Cyclospora* causes prolonged diarrhoea in travellers to the tropics, and is associated with malabsorption of vitamin A and D-xylose, with villous atrophy and crypt hyperplasia in small-bowel biopsy specimens.[30] Cotrimoxazole is effective in the treatment of this condition.[31] Severe diarrhoea with malabsorption has been described in immunocompetent adults with isosporiasis.[32] A 7–10-day course of cotrimoxazole effectively treats isosporiasis in immunologically normal patients[33] but is associated with a high rate of relapse in the immunosuppressed.[34] In the immunosuppressed patients, treatment with cotrimoxazole must be continued for longer periods of time. Microsporidia infections are less common than other protozoan infections but are implicated in self-limited diarrhoeal illness in immunocompetent people in tropical developing nations,[35 36] and as a cause of chronic diarrhoea and malabsorption in patients with HIV infection. Visceral leishmaniaisis is characterised by the presence of parasitised macrophages in the lamina propria of the small intestine with inflammatory cell infiltration, and can cause chronic diarrhoea with malabsorption of vitamin A and D-xylose.[37] Table 1 shows the treatment of these infections.

Helminth infections

Helminth infections are an occasional cause of tropical malabsorption. The most common of these are *Strongyloides stercoralis* and *Capillaria philippinensis*. Infection with *S stercoralis* is common in the tropics and may cause chronic diarrhoea and malabsorption in immunocompetent people.[38] Human T cell lymphotropic virus type 1 infection[39] and steroid usage predispose people to chronic and heavy infection with this parasite. Intermittent or persistent diarrhoea occurs, while steatorrhoea, anaemia and hypoproteinaemia are common.[38 39] Small-bowel barium series may show changes suggestive of mucosal infiltration and ulceration in the duodenum and jejunum.[40] Diagnosis is usually made by examination of faeces for the larvae of the parasite; occasionally, examination of duodenal or jejunal biopsy specimens or a surgical biopsy specimen of the small bowel is required to establish the diagnosis. Treatment with thiabendazole, albendazole or ivermectin has been found to be effective.[41 42] *C philippinensis*, causing intestinal capillariasis, is another helminth that causes malabsorption syndrome, and is common in South East Asia, especially in Thailand and the Philippines,[43 44] but is now reported from other countries including Taiwan, Korea, India, Iran and Egypt. Intestinal capillariasis is associated with protein-losing enteropathy and also malabsorption of fat and D-xylose.[43] Albendazole is currently the drug of choice in the treatment of intestinal capillariasis.[44]

Bacterial infections

Intestinal tuberculosis is common in tropical countries. It may manifest with many clinical syndromes, including obstruction and malabsorption syndromes. Biochemical evidence of malabsorption can be found in many patients with intestinal tuberculosis, even though the patient may not present with a clinical diagnosis of the malabsorption syndrome. In one study, biochemical evidence of malabsorption was found in 75% of patients with intestinal tuberculosis with intestinal obstruction, but in only 40% of patients

Table 1 Treatment of parasites causing tropical malabsorption

Parasitic infection	Treatment
Giardia intestinalis	Metronidazole 400 mg three times daily for a week; tinidazole 2 g single dose; secnidazole 30 mg/kg single dose; nitazoxanide 500 mg twice daily for 3 days; paromomycin 10 mg/kg three times daily for 7 days (pregnancy)
Isospora belli	Cotrimoxazole (160/800 mg) twice daily for 7 days, *followed by one tablet three times a week for 10 weeks; ciprofloxacin 500 mg twice daily for one week, *followed by 500 mg three times a week for 10 weeks
Cryptosporidium parvum	Nitazoxanide 500 mg twice daily for 3–7 days; paromomycin 500 mg 3–4 times daily for 2 weeks
Enterocytozoon bieuneusi	Nitazoxanide 500 mg twice daily for 3–7 days; fumagillin 20 mg three times daily for 2 weeks
Encephalitozoon intestinalis	Albendazole 400 mg twice daily for 2–3 weeks
Cyclospora cayetanensis	Cotrimoxazole (160/800 mg) twice daily for 7 days, *followed by one tablet three times a week for 10 weeks; ciprofloxacin 500 mg twice daily for one week, *followed by 500 mg three times a week for 10 weeks
Leishmania donovani	Miltefosine 100–150 mg daily orally for 4 weeks; liposomal amphotericin B 1–3 mg/kg/day for 5 days; paromomycin 16–20 mg/kg/day for 3 weeks
Strongyloides stercoralis	Thiabendazole 25 mg/kg/12 h for 3 days; albendazole 400 mg twice daily for 3 days; ivermectin 200 μg/kg for 1–2 days
Capillaria philippinensis	Thiabendazole 25 mg/kg/12 h for 20 days; albendazole 400 mg once or twice daily for 10 days

*In underlying HIV infection.

without obstruction.[45] The causes of malabsorption include bacterial overgrowth in a stagnant loop, bile salt deconjugation and diminished absorptive surface due to ulceration and lymphatic obstruction.[46] Considerable abdominal pain in a patient with malabsorption syndrome should alert the clinician to the diagnosis.

Viral infections

Occurrence of pathogen-negative diarrhoea and malabsorption in patients with AIDS has led to speculation that HIV is in itself capable of infecting enterocytes and causing enteropathy. The improvement in diarrhoea and malabsorption with antiretroviral treatment lends credence to this theory.[47]

Inflammation and immune-related causes

Coeliac disease

Coeliac disease (gluten-sensitive enteropathy), hitherto considered uncommon in the tropics, has been described in patients from northern India[48 49] and among the Saharawi in Africa.[50] An intestinal infection may sometimes unmask gluten-sensitive enteropathy, and therefore the diagnosis should be suspected in travellers with diarrhoea and malabsorption on their return to western countries.[51] Differentiation of coeliac disease from tropical sprue hinges on the more profound morphological changes in the jejunal mucosal architecture (complete villous atrophy) in patients with coeliac disease, and the presence of antiendomysial and tissue transglutaminase antibodies among patients with coeliac disease.[52] Clinical and histological responses to gluten withdrawal in patients with coeliac disease as opposed to treatment responses with folic acid, vitamin B_{12} and antibiotics in patients with tropical sprue will also aid differentiation.

Crohn's disease

Crohn's disease is increasingly being diagnosed in tropical countries,[53–55] and is an important differential diagnosis for tuberculosis. Malabsorption in Crohn's disease may occur as a result of several factors.[56] About a third of patients have small-intestinal involvement, and this can reduce the absorptive surface area. Extensive small-bowel resections would have the same effect. Terminal ileal resections can lead to vitamin B_{12} deficiencies and bile salt malabsorption, whereas ileocaecal valve resections result in bacterial overgrowth causing malabsorption. Around 9% of patients with malabsorption were found to have Crohn's disease in an unselected patient series from northern India.[57]

Primary immunodeficiency syndromes

Common variable immunodeficiency occurs sporadically in residents of the tropics, and may present primarily as a malabsorption syndrome.[58] The diagnosis is sometimes first suspected by small-bowel biopsy showing reduced numbers of plasma cells in the lamina propria or by the finding of nodular lymphoid hyperplasia, which is occasionally associated with the disease. The most common infection noted in these patients is with the protozoan *G intestinalis*. Other protozoa may also colonise the small bowel and lead to malabsorption. These include *I belli*, *C parvum* and microsporidia. Selective immunoglobulin (Ig)A deficiency is less common and can be associated with a flat mucosa and giardiasis. Symptomatic chronic infection of the small bowel leads to malabsorption. Bacterial colonisation of the upper small bowel may also occur in some patients with primary immunodeficiency and cause malabsorption. This is identified by quick response to treatment with tetracycline or other antibiotics. Periodic administration of intravenous γ globulin is useful in patients with common variable immunodeficiency.

Malignant causes

Immunoproliferative small intestinal disease and small-bowel lymphoma

Immunoproliferative small intestinal disease (IPSID) was traditionally termed Mediterranean lymphoma but is not uncommon in the tropics.[59–61] The condition usually affects socioeconomically disadvantaged sections of the community. Patients present with chronic diarrhoea and malabsorption in the second and third decades of life. Abdominal pain may be a major complaint. Clubbing of the fingers is characteristic and abdominal masses may be palpated on physical examination. Nutritional deficiencies and a marked weight loss are documented. The disease is caused by clonal proliferation of cells that produce an abnormal α-heavy-chain immunoglobulin, and can be diagnosed by immunoassay for the α-heavy chain in serum. Clonal proliferation may occur secondary to chronic or recurrent infections of the intestine in childhood. Mucosal biopsy of the small intestine is characteristic and shows a dense cellular lymphoplasmacytic infiltrate in the lamina propria leading to effacement of the crypts. Three stages of the disease are noted, ranging from an apparently benign disease (stage A) to a clear lymphoma (stage C). The disease progresses over variable periods of time to the development of lymphoplasmacytic and immunoblastic lymphoma. Staging of the disease by laparoscopy or laparotomy should precede chemotherapy or radiation therapy. Areas of bulky tumour are resected before chemotherapy, and full-thickness biopsy of involved areas of the intestine with biopsy of the enlarged mesenteric nodes is performed. In the premalignant stage (stage A), long-term treatment with antibiotics such as tetracycline may cure the disease. Recently, IPSID was shown to be associated with

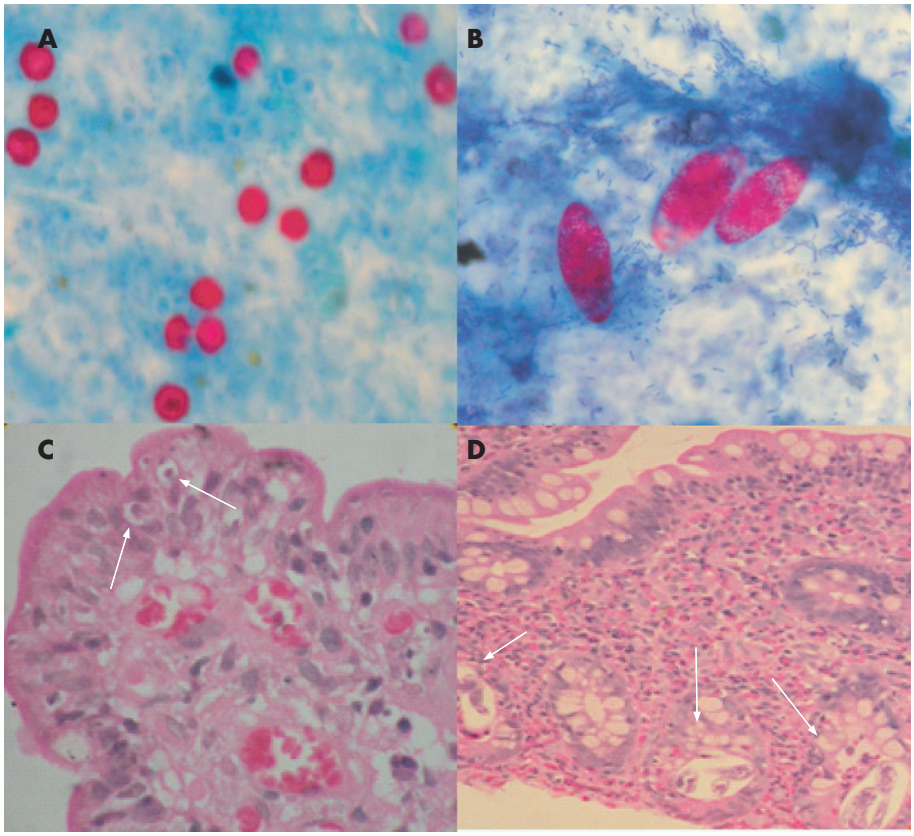

Figure 1 Some parasites that cause malabsorption in tropical countries. Faecal smears stained with modified AFB stain showing (A) *Cryptosporidium parvum* oocysts, 5 m diameter; (B) *Isospora belli* oocysts, 30 m long. Duodenal mucosal biopsy specimens (haematoxylin–eosin staining, ×40) showing (C) microsporidia (arrows) in villous epithelial cells and (D) *Strongyloides stercoralis* larvae (arrows) in the crypt lumen. Images courtesy of Professor Gagandeep Kang and Professor Anna Pulimood.

Campylobacter jejuni infection,[62] suggesting that this was one potential antigenic stimulus driving the uncontrolled proliferation of B cells. Incidence of IPSID is reducing in areas where it was previously prevalent, probably owing to improving hygiene.[63]

Pancreatic disease

Tropical pancreatitis

Idiopathic chronic calcific pancreatitis is endemic in several tropical regions including the Indian subcontinent and southern Africa. Symptoms typically develop in adolescence and the usual presentation is with recurrent abdominal pain attributable to pancreatitis.[64] Exocrine pancreatic insufficiency develops in 25–50% of patients and diabetes mellitus may eventually occur in over a half of those affected. In some patients, presentation is solely with features of chronic diarrhoea and malabsorption due to the exocrine pancreatic insufficiency. Xylose absorption is usually normal in these patients, and faecal fat is grossly increased. Vitamin B_{12} malabsorption may be noted in some people due to lack of pancreatic proteolytic activity and failure to cleave the R protein–vitamin B_{12} complex. A mutation in a serine protease (SPINK1) gene can be detected in 40–50% of patients, and other mutations may explain the remainder.[65 66] Diagnosis is made by the detection of pancreatic calcification on plain abdominal radiographs or ultrasound scans of the abdomen.Occasionally, endoscopic retrograde pancreatography or endoscopic ultrasonography is used to establish the diagnosis. Malabsorption can be treated by an oral dose of a pancreatic enzyme preparation such as Creon with every meal.

PRIMARY MALABSORPTION

Tropical enteropathy

The mucosa of the small intestine of residents of the tropics is structurally different from that of residents of temperate countries. The villi are shorter, crypts are more elongated and there are increased numbers of lymphocytes in the lamina propria.[67 68] This leads to subclinical malabsorption, a condition that has been termed tropical enteropathy. Malabsorption of fat, vitamin B_{12} and xylose, as well as increased mucosal permeability, has been noted in a large number of healthy residents of the tropics.[69 70] About 50% of healthy south Indian villagers had xylose malabsorption, reflecting reduced mucosal surface area in the small intestine; 10% had fat malabsorption and 3% had vitamin B_{12} malabsorption.[67] Similar changes were found in Peace Corps volunteers in rural Pakistan 40% and 48% of whom had malabsorption of xylose and vitamin B_{12}.[71] Affected people are asymptomatic, a major distinction from tropical sprue which leads to overt symptoms of diarrhoea and malnutrition. Tropical enteropathy may represent an adaptation of the gut to frequent intestinal infection.[72] Newborn infants in the tropics have the same villous height as that in infants from temperate regions, but changes connected with tropical enteropathy develop within 2–12 weeks of birth.[73] Bacterial colonisation of the small bowel and isolation of a wide range of pathogens from stool has been noted in healthy asymptomatic people in the tropics.[74] Studies on a cohort of African adults followed sequentially for 3 years showed that changes in tropical enteropathy fluctuated over a 3-year period.[75] Enteropathy was more severe in people with *Citrobacter rodentium* or hookworm infection, suggesting that

intestinal infections may be an important factor. T cells possibly have a role in the development of enteropathy.[76] Genetic factors may be responsible as well, as British Indian and Afro-Caribbean residents in West Birmingham, UK who never returned to their country of origin also showed considerable differences in small-bowel mucosal architecture compared with the indigenous Caucasian residents.[77]

Tropical sprue

Definition

Tropical sprue is an acquired disease of unknown aetiology, characterised by malabsorption, multiple nutritional deficiencies and mucosal abnormalities in the small bowel. The definition of the various clinical syndromes that are together termed tropical sprue is still controversial. Baker and Klipstein[78] suggested that the diagnosis of tropical sprue should be made only when there is malabsorption of two or more unrelated nutrient groups (eg, fat and carbohydrate), and after other known causes of malabsorption have been excluded. Cook[79] proposed the term ''post-infectious tropical malabsorption'' to describe a syndrome of malabsorption in travellers returning to the UK in whom the illness was preceded by an acute diarrhoeal illness and who had evidence of jejunal colonisation with aerobic and anaerobic bacteria.

Epidemiology

Tropical sprue has been described in South and South East Asia, Central America, Venezuela, Colombia and parts of Mexico and the Caribbean islands, but not in Jamaica or in sub-Saharan Africa.[80 81] Endemic sprue was estimated to occur in about 8% of North Americans in Puerto Rico.[82] It was a major cause of morbidity among British troops in Malaysia and Hong Kong in the late 1960s[83] and in American soldiers in Vietnam.[84] Although endemic tropical sprue is now much rarer than before, it still accounts for nearly 40% of malabsorption in both adults and children in south Asia.[57 85 86] Epidemics of tropical sprue were reported in soldiers and prisoners of war in the Indo-Burma region during the Second World War,[6 7] and in American military personnel serving in the Philippines.[87] Epidemics of tropical sprue affecting villagers in southern India were reported between the 1960s and early 1980s but have not been detected since then.[88] The disappearance of epidemic tropical sprue and the decline of sporadic tropical sprue may be secondary to widespread use of antibiotics and to improvements in hygiene and water quality.

Table 2 Summary of clinical manifestations of tropical sprue and their causative factors

Symptom	Cause
Diarrhoea	Malabsorbed nutrients with osmotic diarrhoea; colonic water secretion due to unabsorbed fatty acids
Pale, bulky foul-smelling stool	Fat malabsorption
Borborgymi, abdominal fullness	Carbohydrate malabsorption
Pedal oedema, skin changes	Hypoproteinaemia secondary to loss of mucosal surface, protein loss and pancreatic insufficiency
Pallor	Vitamin B_{12} and folate deficiency, rarely iron deficiency
Angular stomatitis, glossitis	Vitamin B deficiency
Night blindness, corneal xerosis, Bitot's spots	Vitamin A deficiency
Muscle weakness	Hypophosphataemia, hypokalaemia, hypomagnesaemia
Weight loss	Anorexia, malabsorption

Aetiology

The aetiology of tropical sprue remains unknown. The need for prolonged residence in the tropics and the response to antibiotics suggested that persistent intestinal infection was responsible. Bacterial contamination of the small bowel was described in returning expatriates who developed tropical sprue,[89] as well as in the indigenous population from several regions with endemic tropical sprue.[90 91] However, no single causative infectious agent was identified, and the bacteria were of several different kinds, suggesting that bacterial colonisation was secondary to small intestinal stasis.[79] On the other hand, a specific overgrowth of coliforms in the small intestine was described in rural Haitians with tropical sprue.[92] The organisms were *Klebsiella*, *Enterobacter* or *Escherichia coli*, and produced toxins that caused mucosal damage and secretion in intestinal loops of experimental animals.[93] Studies in rural southern India and in South Africa indicated that bacterial colonisation of the small intestine was present not only in patients with tropical sprue but also in apparently healthy people, and the two groups could not be distinguished on the basis of the numbers or kinds of bacteria isolated from the small bowel.[76 94] The presence of bacterial contamination of the proximal small bowel in healthy people was attributed to the contaminated environment. The issue of whether this bacterial colonisation could lead to tropical sprue in those with a genetic predisposition has not been considered, especially as earlier studies predated current understanding on innate immune responses in the gastrointestinal tract. Of 27 Puerto Rican patients with tropical sprue, 25 had at least one human leucocyte antigen of the Aw-19 series. The strongest association was with Aw-31, for which the relative risk was 10.6.[95] A recent study re-evaluated the role of small-bowel bacterial colonisation in patients with tropical sprue. In this study, 10 of 13 patients with sprue had aerobic bacteria in the small intestine in larger numbers (median 3.6×10^4) than patients with irritable bowel syndrome (median 7×10^2); however, there was no uniform pattern of colonisation. The authors postulated that bacterial colonisation was secondary to slowing of small-bowel transit induced by the ileal brake responding to unabsorbed fat.[96] Treatment with tetracycline and folic acid reversed the prolongation of transit in most patients. Similar slowing of small intestinal transit in coeliac disease can be reversed with gluten withdrawal.[97] Viruses have also been implicated in the pathogenesis of tropical sprue. Viral particles resembling human enteric corona viruses have been identified in the stool of patients with tropical sprue.[98] However, the finding of similar viruses in asymptomatic people[99] raises the question of their pathogenicity. Coccidian parasites such as *Cyclospora cayetanensis* might have a role in the initiation of tropical sprue in some patients.[100]

Pathophysiology

Nutrient malabsorption in tropical sprue arises from involvement of both the proximal and distal small intestine. Ultrastructural studies show degenerating cells in the crypts of the small intestine, suggesting stem cell damage.[101] Reduction in the total absorptive surface area as a consequence of villus atrophy and loss of epithelial cell microvilli results in reduced xylose absorption and malabsorption of fat and fat-soluble vitamins. Folate and iron deficiency represent proximal small-bowel involvement, whereas vitamin B_{12} malabsorption reflects terminal ileal involvement. Bile acid malabsorption occurs as a result of terminal ileal involvement and may contribute to diarrhoea. Colonic malabsorption of water and electrolytes contributes considerably to diarrhoea

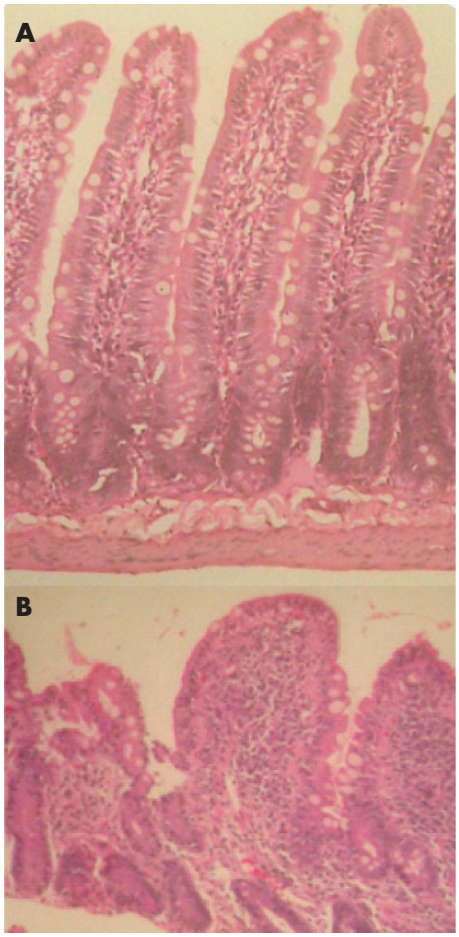

Figure 2 Small-bowel mucosal biopsy in tropical sprue. (A) Normal small-bowel mucosa (haematoxylin–eosin staining (H&E), ×10), showing tall villi and short crypts with a villus:crypt ratio of 4:1. (B) Biopsy specimen from a patient with tropical sprue (H&E, ×10). Villus atrophy, crypt elongation and inflammatory cell infiltration of the lamina propria can be seen. The villus:crypt ratio is reduced to 1.5:1. Images courtesy of Professor Anna Pulimood.

in patients with sprue, and may result from the action of unabsorbed bile acids and free unsaturated fatty acids.[102 103] Lymphocytic infiltration of the colonic mucosa is also seen.[104] Figure 2 shows the haematoxylin–eosin staining of a mucosal biopsy specimen from a patient with tropical sprue.

Clinical manifestations

A typical patient with tropical sprue is an adult who presents with chronic diarrhoea, glossitis, bloating, prominent bowel sounds and weight loss. The signs of nutritional deficiency include pallor due to anaemia; angular stomatitis, cheilitis and glossitis due to vitamin B deficiency; and peripheral oedema and skin and hair changes secondary to hypoproteinaemia. Rarely, vitamin A deficiency may manifest with night blindness and corneal xerosis, while vitamin B_{12} deficiency leads to subacute combined degeneration of the spinal cord. In expatriates, the illness is heralded by acute diarrhoea associated with fever and malaise in the first week. A milder form of chronic diarrhoea, steatorrhoea and a marked weight loss follows this. Some patients may present solely with a specific nutritional deficiency such as megaloblastic anaemia or hyperpigmentation of the skin due to vitamin B_{12} deficiency. Fever, uncommon in Caribbean patients, has been noted in almost a quarter of patients from southern India. Table 2 summarises the clinical manifestations of tropical sprue and their postulated causes.

DIAGNOSIS

The three tests commonly used in investigating absorption are stool fat estimation and absorption of D-xylose and vitamin B_{12}. Two abnormal tests in the appropriate setting are consistent with tropical sprue in the absence of other causes of malabsorption. Quantitative stool fat estimation is the most reliable test of malabsorption in the tropics.[105] As performing this test is difficult, steatorrhoea is often assessed semiquantitatively using Sudan staining of oil (triglyceride) droplets in stool. Although this is useful to detect the increased faecal fat (triglyceride) in patients with chronic pancreatitis, Sudan stain is not sensitive in the diagnosis of tropical sprue, where the faecal fat is in the form of fatty acids rather than triglycerides.[106] The acid steatocrit, which measures fat in stool using its physical properties,[107] has not been assessed in tropical sprue. D-xylose malabsorption is found in about 99% of patients, steatorrhoea is seen in about 90% and vitamin B_{12} malabsorption in 60–90%. Peroral capsule biopsy of the jejunal mucosa has been replaced by endoscopically obtained duodenal mucosal biopsy. It is important to take biopsy specimens from beyond the second part of the duodenum, as villi in the second part may be shorter than they are more distally in the duodenum and in the jejunum. Endoscopically, tropical sprue may resemble coeliac disease, with scalloping of the duodenal mucosa.[108] Endoscopic innovations such as push enteroscopy aid in visualisation of the jejunum, directed biopsy and differentiation of tropical sprue from other diseases.[109] Characteristic histological changes include shortening of the villi, crypt hypertrophy and infiltration of the lamina propria and epithelium by mononuclear cells (fig 1). Total villous atrophy, as reported in coeliac sprue, is rare in tropical sprue.

Treatment

Restoration of fluid and electrolyte balance is necessary in dehydrated patients, and deficiencies of magnesium and potassium need to be corrected in those with longstanding illness. Specific deficiencies of vitamins A and D and the B complex vitamins may be treated with either parenteral or oral supplements. Parenteral vitamin B_{12}, oral folate and iron replacement result in prompt resolution of symptoms of anaemia, glossitis and anorexia, and result in weight gain even before improvement in intestinal absorption.[110] Folate may be depleted both by damage to the host epithelium and by bacterial uptake.[111] Folate supplementation improves macrocytic anaemia and also villous atrophy.[112] Antimicrobial agents are widely used for treatment, and tetracycline 250 mg four times daily (or doxycycline 100 mg once daily) for 3–6 months is the antibiotic of choice. Restriction of long-chain fatty acids in the diet helps to reduce diarrhoea, which is one of the major symptoms. Medium-chain triglycerides may be substituted for long-chain fatty acids. Complete recovery is the rule in the returned traveller. In endemic sprue, relapses are common, occurring in 50% of affected people.

APPROACH TO TROPICAL MALABSORPTION

The list of differential diagnoses in patients with tropical malabsorption is wide and varied. The clinician needs to consider various factors when evaluating such patients. As enteric infections are easily diagnosed and there is recourse to specific treatment, it is appropriate to first screen for protozoan and helminth parasites by stool microscopy. Typically, three faecal samples should be obtained for microscopy, and examined as wet smears after concentration techniques and with special stains (such as safranine

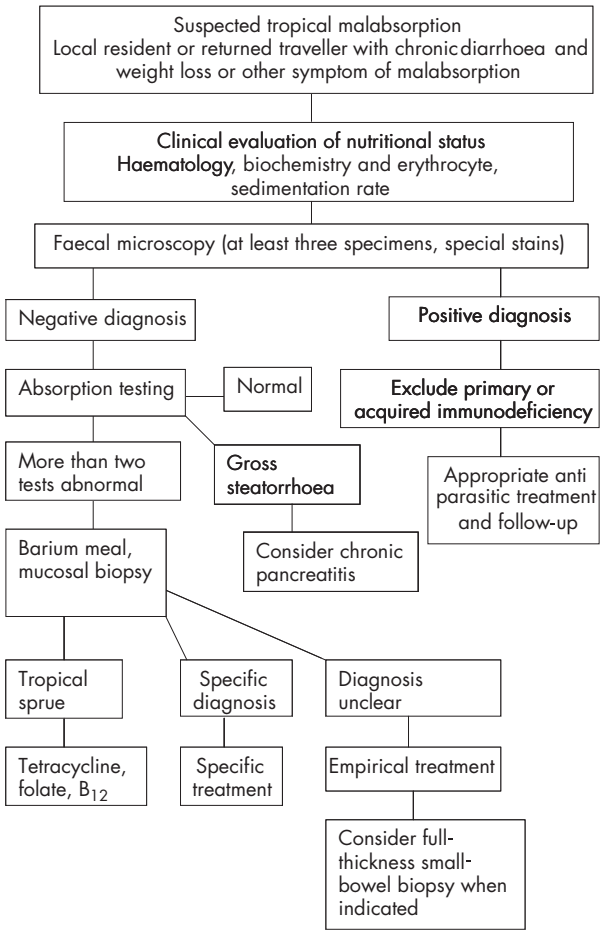

Figure 3 Algorithm for evaluation and management of tropical malabsorption.

methylene blue or modified AFB stains) for the protozoan parasites. Stool cultures are rarely diagnostic in this setting but are performed in selected patients. Testing for HIV infection after counselling is performed when indicated. In a child, it is appropriate to ask for a history of gluten sensitivity and screen for coeliac sprue. Confirming malabsorption is the next step in the process, which involves estimation of faecal fat, D-xylose absorption and vitamin B_{12} absorption. If two of these tests are abnormal, a small-bowel biopsy series and deep duodenal biopsy are indicated. Diagnosis of tropical sprue, parasitic disorders, IPSID and other specific conditions can be made on the basis of biopsy results. If the diagnosis remains unclear at this stage, with biochemical evidence of malabsorption and mucosal abnormality on the small-bowel biopsy series, and no relief with symptomatic therapy, biopsy from deeper segments of the bowel may be indicated. In this situation, double-balloon enteroscopy or laparoscopy and full-thickness biopsy of the small bowel may be helpful. Figure 3 summarises this approach to tropical malabsorption.

Tropical malabsorption comprises a variety of disorders ranging from mildly symptomatic disease to life-threatening illnesses. A structured approach to diagnosis and therapy is outlined.

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MULTIPLE-CHOICE QUESTIONS (TRUE (T), FALSE (F); ANSWERS AFTER THE REFERENCES)

1. Which of the following statements are true regarding tropical enteropathy?

   A. Most of the patients are symptomatic
   B. People living in the tropics have longer villi than those residing in temperate climates
   C. Tests of absorption may be abnormal in a proportion of patients
   D. Lamina propria inflammation is never seen in these patients
   E. All patients should be aggressively treated with antibiotics

2. Which of the following statements are true?

   A. Tropical sprue is seen only in visitors to the tropics
   B. Tropical sprue can occur in an epidemic form
   C. Tropical sprue is seen universally in all tropical regions
   D. Latent sprue can present after many years
   E. Sporadic sprue is not seen in the tropics

3. Which of the following statements are true regarding the pathogenesis of tropical sprue?

   A. Bacterial colonisation of the small intestine is seen in patients with tropical sprue
   B. Bacterial strains in tropical sprue tend to be more toxigenic
   C. Enteroglucagon is implicated in the pathogenesis of sprue
   D. Coccidian pathogens have been found in biopsy specimens with tropical sprue
   E. Small-bowel transit time is prolonged in tropical sprue

4. Which of the following statements are true regarding tropical sprue?

   A. Villous hypertrophy and crypt degeneration are seen in patients with tropical sprue
   B. The stem cell compartment of the epithelial cell layer is affected
   C. There is net secretion of fluids in tropical sprue
   D. Microvilli are affected in tropical sprue
   E. Colonic absorption of water remains unaffected in tropical sprue

5. Which of the following statements are true?

   A. The morphological changes in the mucosa in intestinal infection mimic tropical sprue
   B. Opportunist infections in AIDS do not cause malabsorption

C. Severe histological changes are not seen in tropical sprue compared with coeliac sprue
D. Immunoproliferative small intestinal disease is a localised disease of the small intestine
E. Tuberculosis can present as a malabsorption syndrome

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ANSWERS (F, FALSE, T, TRUE)

1. (A) F (B) F (C) T (D) F (E) F
2. (A) F (B) T (C) F (D) T (E) F
3. (A) T (B) T (C) T (D) F (E) T
4. (A) F (B) T (C) T (D) T (E) F
5. (A) T (B) F (C) T (D) F (E) T